

## A Comparison of Nortriptyline and Amitriptyline in Depression

JOHN T. ROSE, M. R. LEAHY, IAN C. A. MARTIN and T. T. WESTHEAD

Nortriptyline (Allegron, Aventyl) is the demethylated metabolite of amitriptyline. Preliminary trials by Bennett (1962), Oltman *et al.* (1963) and Leahy *et al.* (1964) indicated that it might be an effective anti-depressant. Forrest *et al.* (1964) found that it compared favourably with amitriptyline, a widely used anti-depressant of established efficacy. This investigation also compares nortriptyline with amitriptyline.

### METHOD

The subjects were 37 in-patients and 13 outpatients (36 female, 14 male) of a psychiatric unit, suffering from primary depressive disorders and classified into reactive and endogenous depressions. No selection was made regarding severity of illness, but patients over the age of 65 years were excluded. Each patient was assessed independently by two clinicians, using an appropriate rating scale (Hamilton, 1960), the sum of both assessments being taken as the score for the patient. Assessments were made initially and after 2 and 4 weeks treatment; in addition, on ordinary clinical grounds, the patient was finally noted as Recovered (marked improvement with few or no symptoms) or Not Recovered (partial or no remission of symptoms).

Treatment was randomly allocated so that equal numbers of patients received each drug. Amitriptyline was given in doses of 10 mg. q.i.d. for the first week, 25 mg. q.i.d. for the second week and thereafter 50 mg. t.i.d. Nortriptyline was given in doses of 10 mg. q.i.d. for the first week, 20 mg. q.i.d. for the second week and thereafter 25 mg. q.i.d. (the maximum dose recommended by the manufacturer). Since many patients with depression also show considerable anxiety or agitation, it is a common practice of the authors to give a

tranquillizer as well as an anti-depressant drug; all patients, therefore, received promazine hydrochloride 50-100 mg. t.i.d. in addition. Psychotherapy was given at the level indicated.

### RESULTS

#### (a) Over-all Outcome

Table I shows the rating scale scores before and after treatment. The patients have a mean initial score of 42.6 points; the mean 2 and 4 weeks scores are 19.4 and 13.7 respectively, which indicates considerable improvement in the group as a whole. Regarding the two treatments, none of the scores differ at a significant level, but those of the amitriptyline group are consistently lower. Over-all comparison then, reveals no significant difference in response to treatment.

#### (b) Outcome of Diagnostic Groups

In Table II the two drug groups are compared with regard to diagnostic classification by the method of analysis of variance. No differences at a significant level are found between the groups, although that for the 4 week scores just fails to reach significance ( $0.1 > P > 0.05$ ). However, the outcome for endogenous cases receiving amitriptyline is consistently better than that for all other groups. Another feature of interest is the very similar response of both reactive and endogenous depressions to nortriptyline.

The outcome for each of the diagnostic groups was further investigated by comparing all possible pairs of groups, using the Student *t*-test. None of the six tests on the 2 week scores shows a significant difference. On the 4 week scores, however, the mean for the endogenous group receiving amitriptyline is significantly lower than that for all other groups; the reactive

and endogenous groups receiving nortriptyline do not differ significantly from each other nor from the reactive cases on amitriptyline.

(c) *Clinical Assessment*

On this depended whether the patient was discharged or his treatment changed. Table III shows the results. The 24 recovered cases consisted of 10 on nortriptyline and 14 on amitriptyline; this difference is not significant. Considering the diagnostic groups, the response to nortriptyline is not significantly different as between reactive and endogenous cases; with amitriptyline however, it is clear that the recovered patients are almost all of the endo-

genous group, this difference in response reaching a significant level ( $\chi^2 = 4.54$ , df = 1,  $P < 0.05$ , with Yate's correction). These results again emphasize the superior outcome of endogenous depressions treated with amitriptyline, the considerably poorer response of reactive cases to this drug, and the intermediate outcome of both reactive and endogenous depressions treated with nortriptyline.

(d) *Side-Effects*

Included here are only those conditions spontaneously complained of by the patients or observed by the nursing and medical staff. They occurred in 26 patients (52 per cent) but on the

TABLE I

			Nortriptyline	Amitriptyline	Total
No. of cases ..	..	..	25	25	50
Mean Initial Scores	..	..	42.4 $t < 1$	42.8 $P = N.S.$	42.6
Mean 2 week Scores	..	..	22.0 $t = 1.68$	16.8 $P = 0.10$	19.4
Mean 4 week Scores	..	..	15.5 $t = 1.07$	12.3 $P = N.S.$	13.7

TABLE II

		Nortriptyline		Amitriptyline	
		Reactive	Endogenous	Reactive	Endogenous
No of cases ..	..	14	11	9	16
Mean Initial Scores	..	41.5	43.3 $F < 1$	45.0 $P = N.S.$	41.6
Mean 2 week Scores	..	22.3	21.6 $F = 1.31$	20.3 $P = N.S.$	14.9
Mean 4 week Scores	..	15.3	15.6 $F = 2.62$	19.2 $0.1 > P > 0.05$	8.5

TABLE III

			Recovered	Not Recovered	Total
Nortriptyline					
Reactive ..	..	..	5	9	14
Endogenous ..	..	..	5	6	11
Amitriptyline					
Reactive ..	..	..	2	7	9
Endogenous ..	..	..	12	4	16
Total ..	..	..	24	26	50

whole did not prove troublesome. With nortriptyline 11 patients had side-effects—4 dryness of mouth, 3 tremor of upper limbs, 2 shakiness of legs and 2 drowsiness; in 2 cases a temporary reduction in dosage was necessary. With amitriptyline, 15 patients had side-effects—6 dryness of mouth, 5 drowsiness, 3 faintness and 1 constipation; 3 cases needed a temporary reduction in dosage. Most of these effects occurred on maximum dosage, and only a few were multiple. All patients received promazine hydrochloride in addition to their anti-depressant drug and therefore any side-effects should strictly be regarded as resulting from the combined therapy.

#### DISCUSSION

This was not a double-blind trial, and since the criteria of improvement depended on assessments made by the investigators some reservation must be applied to the results. However, it is reasonable to suppose that the double assessment would minimize any observer bias. Furthermore, it might be argued that the design of this investigation does have the merit of approximating closely to the actual therapeutic situation.

Considering each drug group as a whole, no significant difference in outcome was found between treatment with nortriptyline and amitriptyline, although the latter drug was consistently more effective. This finding is substantially in line with that reported by Forrest *et al.* (1964), but these authors found a different trend, nortriptyline having the better outcome, although not significantly so. In the latter investigation severely depressed patients were excluded, drug dosage was not standardized, no additional therapy was given and the response to treatment was assessed after only 14–18 days. These differences in experimental design might account for the differing trends.

Relating outcome to the diagnostic groups, under the conditions of the trial these two drugs

appear to have different patterns of response; amitriptyline is most effective on endogenous depressions whilst nortriptyline is equally effective on both types of depression, but to a lesser extent. However, it must be noted that the maximum dose of nortriptyline was only two-thirds that of amitriptyline.

Although the incidence of side-effects was slightly lower in patients treated with nortriptyline, neither drug appears to have any definite advantage in this matter.

#### SUMMARY

Nortriptyline was compared with amitriptyline in the treatment of 50 patients suffering from primary depressive disorders and classified as reactive and endogenous depressions. All patients received promazine hydrochloride in addition to specific anti-depressant therapy and were assessed initially and after 2 and 4 weeks treatment.

Comparison without diagnostic classification showed no significant difference in outcome between the two drugs, although amitriptyline was consistently more effective. The outcome of endogenous depressions treated with amitriptyline was significantly better than all other diagnostic groups; reactive depressions on this drug showed the least improvement but not significantly inferior to reactive and endogenous cases on nortriptyline, the latter two groups having almost identical outcomes. Side-effects were least numerous with nortriptyline and on the whole interfered little with treatment.

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